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DANN, DORFMAN, HERRELL & SKILLMAN
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SUITE 2400
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AEDER, SEAN E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,392	YU ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-14,16-20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23-26* is/are allowed.

6)☒ Claim(s) *1,2,5-14,16-20,22 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 12/6/07 in response to the Office Action of 9/7/07 are acknowledged and have been entered.

Claims 1, 2, 5-14, 16-20, and 22-27 are pending.

Claims 1, 2, 5-14, 16-20, and 22-27 have been amended by Applicant.

Claims 1, 2, 5-14, 16-20, and 22-27 are currently under examination.

The following Office Action contains New Rejections.

Objections Withdrawn

The objection to the specification for containing embedded hyperlinks and/or other form of browser-executable code is withdrawn.

The objections to claims 12, 22, and 27 are withdrawn.

Rejections Withdrawn

The rejection of claim 1 and dependent claims 2 and 5-11 under 35 U.S.C. 112, second paragraph, for being incomplete for omitting essential steps, is withdrawn.

The rejection of claims 2, 5, 8, 9, 11 and dependent claims 6, 7, and 10 under 35 U.S.C. 112, second paragraph, for reciting: "A method according to claim 1...", is withdrawn.

The rejection of claim 6 and dependent claim 7 under 35 U.S.C. 112, second paragraph, for reciting: "A method according to claim 5…", is withdrawn.

The rejection of claim 6 and dependent claim 7 under 35 U.S.C. 112, second paragraph because of a lack of antecedent basis for a limitation, is withdrawn.

The rejection of claim 7 under 35 U.S.C. 112, second paragraph, for reciting: "A method according to claim 6…", is withdrawn.

The rejection of claim 8 under 35 U.S.C. 112 second paragraph, as being incomplete for omitting essential steps, is withdrawn.

The rejection of claim 10 under 35 U.S.C. 112, second paragraph, for reciting: "A method according to claim 9…", is withdrawn.

The rejection of claims 13-15 under 35 U.S.C. 112, second paragraph, for reciting: "Apparatus according to claim 12…", is withdrawn.

The rejection of claims 17-20 and 22 under 35 U.S.C. 112 second paragraph, for reciting: "A kit according to claim 16…" or "A kit according to claims 16…", is withdrawn.

The rejection of claim 22 under 35 U.S.C. 112 second paragraph, because it is unclear what is meant by "they", is withdrawn.

The rejection of claims 24-26 and dependent claim 27 under 35 U.S.C. 112 second paragraph, for reciting: "A method according to claim 23...", is withdrawn.

The rejection of claim 27 under 35 U.S.C. 112 second paragraph, for reciting: "A method according to claim 26...", is withdrawn.

The rejection of claim 27 under 35 U.S.C. 112 second paragraph, as being incomplete for omitting essential steps, is withdrawn.

The rejection of claims 12 and 13 under 35 U.S.C. 102(e) is withdrawn. However, claims 16-20 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Wirtz et al (US 2004/0018525 A1; filed 5/9/03), as indicated below.

Response to Arguments

Specification

The specification remains rejected to for the reasons stated in the Office Action of 9/7/07 and for the reasons set-forth below.

The Office Action of 9/7/07 contains the following text:

"The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. The claims define the

invention by Unigene numbers corresponding to gene descriptions (see Table S6, in particular), which are not sequences provided in the specification. The sequences of the Unigene numbers corresponding to gene descriptions are essential to practice the claimed invention, and the only disclosure of the sequences is made by references to published information outside of the specification. Therefore, information essential to practice the invention is incorporated by reference. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973)."

In the Reply of 12/6/07, Applicant argues that the sequences of the Unigene numbers are not absolutely required to make or use the instantly claimed invention. Applicant further sates that the instant invention does not concern the identification of new genes but rather the finding that known genes are related to the prognosis of patients with breast cancer. Applicant further states that Table S6 identifies known genes through a gene description, known biological process, and Unigene number. Applicant further states that a skilled artisan is capable of obtaining a nucleotide sequence of genes listed in Table S6 through any source to make and use the instantly claimed invention. Applicant concludes that the specific sequences are nonessential material for making and using the instant invention and can, therefore, be incorporated by reference from a non-patent publication.

The amendments to the claims and the arguments found in the Reply of 12/6/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the sequences of the Unigene numbers are not absolutely required to make or use the instantly claimed invention and that the instant invention does not

concern the identification of new genes but rather the finding that known genes are related to the prognosis of patients with breast cancer, the instant claims are drawn to methods comprising measuring levels of nucleic acid expression products. Further, the instant claims are drawn to products for detecting nucleic acid expression products. One of skill in the art would recognize that the structure of a nucleic acid expression product is essential for producing reagents that would measure the levels of or detect said nucleic acid expression product. One of skill in the art would further recognize that the sequence of a nucleic acid expression product is the essential structural characteristic to identify said nucleic acid expression product. The instant specification makes reference to Unigene numbers as an indication of the sequences of the nucleic acid expression products relating to the instant claims. Therefore, the sequences of the Unigene numbers, which describe the structure of nucleic acid expression products, are absolutely required and essential to make or use the instantly claimed invention.

In regards to the arguments that Table S6 identifies known genes through a gene description, known biological process, and Unigene number and that a skilled artisan is capable of obtaining a nucleotide sequence of genes listed in Table S6 through any source to make and use the instantly claimed invention, the nucleotide sequences of genes listed in Table S6 are defined by Unigene numbers. For the reasons discussed above, Unigene numbers corresponding to gene descriptions are essential to practice the claimed invention, and the only disclosure of the sequences is made by references to published information outside of the specification. Therefore, information essential to practice the invention is incorporated by reference. Applicant is required to amend the

disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 13, 14, 17, and 24 remain rejected under 35 U.S.C. 112, second paragraph, for the reasons stated in the Office Action of 9/7/07 and for the reasons set-forth below.

The Office Action of 9/7/07 contains the following text:

"...for attempting to claim methods or products by making reference to a table within the specification (Table S6). 35 U.S.C. 112, second paragraph, requires that the *claims* claim the subject matter. Reference to a table within the disclosure by a claim is not an acceptable method of claiming subject matter under 35 U.S.C. 112, second paragraph."

In the Reply of 12/6/07, Applicant argues that cites MPEP 2173.05(s) and states that referencing a table in a claim is permissible under certain circumstances. Applicant further argues that it is not practical to list all genes of Table S6 in the claims and that it is more concise to incorporate the table by reference rather than duplicating the table in the claim.

The arguments found in the Reply of 12/6/07 have been carefully considered, but are not deemed persuasive. In regards to the arguments that MPEP 2173.05(s) states that referencing a table in a claim is permissible under certain circumstances, that it is not practical to list all genes of Table S6 in the claims, and that it is more concise to incorporate the table by reference rather than duplicating the table in the claim, MPEP 2173.05(s) states that said circumstances are those where there is "no practical way" to define the invention in words and where it is more concise to incorporate by reference rather than duplicating a drawing or table in a claim. In the instant case, listing the genes of Table 6 in the claims is a practical way to define the invention in words.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-11, and 27 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons stated in the Office Action of 9/7/07 and for the reasons set-forth below.

The Office Action of 9/7/07 contains the following text:

"...the specification, while being enabling for a method for determining the prognosis of a first patient with breast cancer comprising comparing the polynucleotide expression levels of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 in a breast tumor sample from said first patient to the expression levels of the polynucleotides of said set of genes in a breast tumor sample from a second patient, wherein a first patient with higher levels of expression of polynucleotides of said set of genes has a poorer prognosis **than a second patient with lower levels of expression of said set of genes** (see page 4 and Table S6, in particular), the specification does not reasonably provide enablement for a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of

expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) or a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) and a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27).

The specification teaches a method for determining the prognosis of a first patient with breast cancer comprising comparing the polynucleotide expression levels of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 in a breast tumor sample from said first patient to the expression levels of the polynucleotides of said set of genes in a breast tumor sample from a second patient, wherein a first patient with higher levels of expression of polynucleotides of said set of genes has a poorer prognosis than a second patient with lower levels of expression of said set of genes (see page 4 and Table S6, in particular). The specification does not demonstrate that an analysis of polypeptide expression of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 would predictably determine a prognosis.

The state of the prior art dictates that if expression of a molecule, such as a specific polynucleotide, is to be used as a surrogate for a particular prognostic state, some prognostic state must be identified in some way with expression of said molecule. There must be some expression pattern that would allow expression of the molecule to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992,

52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the molecule's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use expression of the molecule in as an indication of a particular prognosis without undue experimentation.

Further, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Thus, the predictability of protein translation and its possible utility as a prognostic cannot predictably be determined by levels of mRNA expression due to the multitude of

homeostatic factors affecting transcription and translation. Thus, information obtained from expression profiles of mRNA expression products, such as expression products of adenine phosphoribosyltransferase genes, MCM4 minichromosome maintenance deficient 4 (S. cervisiae) genes, exonuclease 1 genes, Metallothionein 1H-like protein genes, and clone IMAGE: 5270727 genes, only serves as the basis for further research on the observation itself and is not predicative of polypeptide expression levels.

The level of unpredictability for determining a particular prognosis based on expression levels of genes is quite high. Since neither the specification nor the prior art provide evidence that a measurement of just any type of expression levels of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 is predictably indicative, in every way, of every prognosis, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Further, since neither the specification nor the prior at provide evidence that a comparison of just any type of expression profiles of just any first and second tumour samples of known prognoses would be indicative of, in every way, the prognosis of a first breast tumour sample, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient "based on", in every way, just any type of expression level in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, and optionally comprising determining ER and/or Erb2 status of the tumour sample (see claim 1) and a method of determining, in just any way, the prognosis of a first breast tumour sample by comparing just any type of expression profiles of just any first and second tumour samples of known prognoses (see claim 27), and Applicant has not enabled said methods because it has not been shown that (1) any expression levels of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 are predictably indicative, in every way, of every prognosis or (2) that a comparison of expression profiles of just any first and second tumour samples of known prognoses would be indicative of, in every way, the prognosis of a first breast tumour sample.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed."

In the Reply of 12/6/07, Applicant amended the claims to being directed to

"nucleic acid" expression products.

The amendments to the claims and the arguments found in the Reply of 12/6/07 have been carefully considered, but are not deemed persuasive. Amendments directing the claims to "nucleic acid" expression products are acknowledged. However, the claims remain directed to methods wherein a patient having "higher levels" of the recited nucleic acid expression products, *as compared to any other level*, indicates that a patient "has a poorer prognosis" than *anyone else*. In view of Tockman et al, one of skill in the art would recognize that just any determination of "higher" levels of the recited nucleic acid expression products would predictably indicate that a patient has a poorer prognosis than anyone else (including patients with advanced cancers unrelated to breast cancer). In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed. As indicated in the Office Action of 9/7/07, while being enabling for a method for determining the prognosis of a first patient with breast cancer comprising comparing the polynucleotide expression levels of a set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727 in a breast tumor sample from said first patient to the expression levels of the polynucleotides of said set of genes in a breast tumor sample from a second patient, wherein a first patient with higher levels of expression of polynucleotides of said set of genes has a poorer prognosis **than a second patient with lower levels of expression of said set of genes** (see page 4 and Table S6, in

particular), the specification does not reasonably provide enablement for a method for determining the prognosis of a patient with breast cancer comprising assigning a prognosis to the patient based on polynucleotide expression levels in a breast tumour of said patient of a prognostic set of genes comprising adenine phosphoribosyltransferase, MCM4 minichromosome maintenance deficient 4 (S. cervisiae), exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, wherein just any determination of "higher" levels of the recited nucleic acid expression products would predictably indicate that a patient has a poorer prognosis than anyone else (including patients with advanced cancers unrelated to breast cancer).

Further, in regards to methods of determining the prognosis of a first breast tumour sample by comparing polynucleotide expression profile of a first tumour sample with a polynucleotide expression profile of a second tumour sample of known prognosis "wherein a match of said first and second expression profile indicates said known prognosis" (see amended claim 27), the term "match" broadly reads on "any comparison". Clearly, just any comparison between comparing polynucleotide expression profile of a first tumour sample with a polynucleotide expression profile of a second tumour sample of known prognosis would not indicate said known prognosis, as tumors from patients with a poor prognosis would be compared with ("matched" with) tumors from patients with a good prognosis.

Further, in regards to methods of claim 1 wherein a breast tumor sample is classified as being either high Nottingham Prognostic Index (NPI), low NPI, good prognosis, or bad prognosis based on "upregulation" or "downregulation" of particular

nucleic acid expression products (see amended claim 8), claim 1 does not recite a method of detecting "upregulation" or "downregulation" of nucleic acid expression products. Rather, claim 1 recites a method directed to "levels" of nucleic acid expression products. Further, the claims do not recite as compared to what "upregulation" or "downregulation" of nucleic acid expression products in a sample is determined. Just any determination of "upregulation" or "downregulation" of nucleic acid expression products has not been demonstrated as a marker of NPI or prognosis. The state of the art, such as the teachings of Tockman et al discussed in the Office Action of 9/9/07, is that one of skill in the art would require a demonstration that just any determination of "upregulation" or "downregulation" of the recited nucleic acid expression products demonstrates either high Nottingham Prognostic Index (NPI), low NPI, good prognosis, or bad prognosis as claimed in order to predictably perform the claimed method wherein any determination of "upregulation" or "downregulation" of the nucleic acid expression products recited claims is indicative of either high Nottingham Prognostic Index (NPI), low NPI, good prognosis, or bad prognosis as claimed. Such a demonstration has not been presented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 16-20 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Wirtz et al (US 2004/0018525 A1; filed 5/9/03), for the reasons stated in the Office Action of 9/7/07 and for the reasons set-forth below.

Claim 16 is drawn to a kit comprising a plurality of nucleic acid binding members capable of specifically binding to nucleic acid expression products of a prognostic set of genes and a detection reagent, wherein the prognostic set includes adenine phophoribosyltransferase, MCM4. exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, wherein said kit optionally comprises the apparatus of claim 12. It is noted that claim 16 does not require that said kit comprise nucleic acid binding members for all of the expression products recited in claim 16; rather, said kit may comprise nucleic acid binding members for as few as two expression products recited in claims 16 or "a plurality" of nucleic acid binding members for a single type of expression product recited in claim 16. Claim 17 is drawn to the kit of claim 16, wherein the prognostic set comprises at least 10 genes of Table S6. Claim 18 is drawn to the kit of claim 16, further comprising a data analysis tool, wherein the data analysis tool is a computer program. Claim 19 is drawn to the kit of claim 18, wherein the data analysis tool comprises an algorithm adapted to discrimination between expression profiles of tumours with differing prognoses. Claim 20 is drawn to the kit of claim 16, comprising expression profiles from breast tumor samples with known prognoses and/or expression profiles characteristic of a particular prognosis. Claim 22 is drawn to a kit comprising a

plurality of nucleic acid binding members capable of specifically binding to nucleic acid expression products of genes of a prognostic set of genes and a detection reagent, wherein the prognostic set includes adenine phophoribosyltransferase, MCM4. exonuclease 1, Metallothionein 1H-like protein, and clone IMAGE: 5270727, wherein said binding members are nucleotide primers capable of binding to the nucleic acid expression products of the genes of the prognostic set such that the nucleic acid expression products can be amplified by PCR. It is noted that claim 22 does not require that said kit comprise nucleic acid binding members for all of the expression products recited in claim 22; rather, said kit may comprise nucleic acid binding members for as few as two expression products recited in claims 22 or "a plurality" of nucleic acid binding members for a single type of expression product recited in claim 22.

Wirtz et al teaches a prognostic set for determining the prognosis of a patient with breast cancer (see the Affymetrix U133 apparatus taught at paragraph 487 and the methods of Example 1, in particular). As indicated by the instant specification (see page 23, in particular) and as taught at www.affymetrix.com as of 8/26//07, the Affymetrix U133 apparatus comprises a nucleic acid microarray wherein the binding members are nucleic acid sequences designed to detect polynucleotide expression of tens of *thousands* of genes, including the following genes: adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; and Metallothionein 1H-like protein. Wirtz et al further teaches a U133 kit comprising a solid support which are attached binding members for assigning a prognosis to a patient with breast cancer, said kit comprising a plurality of

binding members capable of specifically binding to expression products of genes of a prognostic set of genes and a detection reagent, wherein the prognostic set includes adenine phosphoribosyltransferase; MCM4 minichromosome maintenance deficient 4 (S. cervisiae); exonuclease 1; and Metallothionein 1H-like protein (see paragraphs 304-316 and the U133 chip database found as of 8/26//07 at www.affymetrix.com, in particular). Further, said U133 apparatus taught at paragraph 487 comprises a prognostic set that comprises at least 5, 10, 20, 30, 40, 50, 60 or all of the genes of Table S6 (see page 74 of the instant specification or compare genes of Table S6 to the U133 chip database found as of 8/26//07 at www.affymetrix.com). Wirtz et al further teaches said kit comprising nucleotide primers "capable of" binding to the expression products of the genes of the prognostic set "such that" they can be amplified by PCR (see paragraph 484, in particular). Wirtz et al further teaches said kit further comprising a data analysis tool, wherein the data analysis tool is a computer program (paragraphs 317-339, in particular). Wirtz et al further teaches said kit wherein said data analysis tool comprises an algorithm adapted to discriminate between expression profiles of tumours with differing prognosis (paragraph 336, in particular). Wirtz et al further teaches said kit comprising the expression profiles from breast tumour samples with known prognoses and/or expression profiles characteristic of a particular prognosis (see paragraphs 336, paragraph 463, and Example 1, in particular).

In the Reply of 12/6/07, Applicant amended claim 12 and indicates claims 16-20 require a solid support that houses binding members to no more than 500 different genes and that Wirtz et al does not teach an apparatus that houses binding members to

no more than 500 different genes. In regards to claim 22, Applicant argues that Wirtz et al fails to teach PCR primers.

The amendments to the claims and the arguments found in the Reply of 12/6/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that claims 16-20 require a solid support that houses binding members to no more than 500 different genes and Wirtz et al does not teach an apparatus that houses binding members to no more than 500 different genes, Applicant's argument is not in commensurate with the scope of the claims. The solid supports encompassed by claims 16-20 do not require a solid support that houses binding members to no more than 500 different genes. Note that claims 16-20 are not dependent upon claim 12 and do not require limitations recited in claim 12.

In regards to the argument that Wirtz et al fails to teach PCR primers, the polynucleotides of the U133 kit taught by Wirtz et al would bind the recited polynucleotides and function as PCR primers.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon adding the limitation that the claimed apparatus houses binding members to no more than 500 different genes, amended claims 12-14 are rejected under 35

U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention is identified by Unigene numbers corresponding to gene descriptions (see Table S6, in particular), which are not sequences provided in the specification. The sequences of the Unigene numbers corresponding to gene descriptions are essential to practice the claimed invention (see objection above), and the only disclosure of the sequences is made by references to published information outside of the specification. The sequences corresponding to Unigene numbers of Table S6 are critical or essential to the practice of the invention, but not included in the claim(s) and are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In order to practice the invention, one of skill has to know the sequences of the expression products encompassed by the claims. Note the objection to the specification above. An amendment accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application would obviate this part of rejection. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Allowable Subject Matter

Claims 23-26 are allowed.

Summary

Claims 1, 2, 5-14, 16-20, 22, and 27 are rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/MISOOK YU/
Primary Examiner, Art Unit 1642